

Applicants: Wybe Martin Kast et al.  
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### REMARKS

Claims 2, 4-18 and 25 are pending and under examination in the subject application. By this Amendment, applicants have amended claims 5, 6, 8, 10, 12, 14 and 16 and have canceled claims 17 and 18. Accordingly, claims 2, 4-16 and 25 will be pending and under examination in the subject application upon entry of this Amendment. In view of the remarks below, applicants maintain that the Examiner's rejections have been overcome, and respectfully request that they be withdrawn.

### Formalities

The Examiner states that the information disclosure statement filed January 4, 1994 fails to comply with 37 C.F.R. §1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in §1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. Specifically, the Examiner states that references EP0375555 and EP0456197 have not been considered as to the merits.

In response, applicants direct the Examiner's attention to the April 5, 1995 Communication submitted to the U.S. Patent Office in connection with this application. The Communication includes concise explanations of the relevance of each references cited in the Information Disclosure Statement, including references EP0375555 and EP0456197. Applicants attach hereto a copy of the Communication as **Exhibit 1**.

Accordingly, applicants submit that the requirements of 37 C.F.R. §1.98(a)(3) have been met and request that the Examiner withdraw the objection, consider the references, and make them of record in this application.

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**Rejection under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 2, 4-18 and 25 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As the Examiner's concedes on page 3 of the June 14, 1996 Office Action, the disclosure is enabled for the subject matter as provided in claim 25, i.e. "for nonapeptide sequences from E6 and E7 genes of HPV16 or HPV18, and MHC-I class molecules as specifically taught in the specification." Therefore, applicants understand the instant rejection to be to the pharmaceutical composition claims, i.e. claims 16-18.

In response, applicants respectfully traverse the Examiner's rejection. The test for enablement is whether one skilled in the art could, at the time of the invention, make and use the claimed invention based on the disclosure and the information known in the art without undue experimentation. Applicants maintain that the claimed invention satisfies the test for enablement, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

The subject invention encompasses peptides comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein the amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV or HPV 18 and wherein the nonapeptide has the ability to bind in the grooves on top of the human major histocompatibility complex (MHC) Class I molecule, as well as pharmaceutical compositions comprising this nonapeptide. This invention is based, at least in part, on applicants' discovery of exact HLA class I binding peptides of HPV16 and HPV18 with CTL inducing properties.

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In support of the rejection, the Examiner states that the specification does not provide sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases. The Examiner further alleges that although applicants have cancelled the rejected method claims, the pharmaceutical composition claims as written suggest the composition would be administered to a subject.

In response, but without conceding the correctness of the Examiner's rejection, applicants note that pharmaceutical composition claims 17 and 18 have been cancelled, thereby rendering the rejection to these claims moot. Applicants further note that the remaining pharmaceutical composition claim 16 has been amended to recite "an effective amount," rather than "prophylactically or therapeutically effective amount." Applicants maintain that peptides that bind to MHC-I are by definition capable of eliciting a cellular response when present. This is inherent in the workings of the immune system and well known to one skilled in the pertinent art. An immune response is automatically triggered upon presentation of a peptide by MHC-I. Accordingly, claim 16 as amended does not require a prophylactic or therapeutic effect, thereby obviating the Examiner's rejection.

The Examiner further states that the scope of claims reciting "a fragment, homolog, isoforms, derivative, genetic variant or conservative variant" is not supported by the specification as it does not disclose the general tolerance to and extent of modification, specific positions and regions of the sequence(s) which can be predictably modified, the critical regions and what variants can be made that retain the biological activity of the intact protein. In response, but without conceding the correctness of the Examiner's rejection, applicants note that claims 5, 6, 8, 10, 12 and 14 have been amended thereby obviating the Examiner's rejection.

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Accordingly, applicants maintain that the specification coupled with the information known in the art clearly enables one skilled in the art to practice the claimed invention. In view of these remarks, applicants maintain that claims 2, 4-16 and 25 satisfy the requirements of 35 U.S.C. §112, first paragraph, and submit that the rejection can be withdrawn.

**Rejection under 35 U.S.C. §112, second paragraph**

The Examiner rejected claims 12 and 14 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that the claims are indefinite for being in improper Markush format.

In response, but without conceding the correctness of the Examiner's rejection, applicants note that claims 12 and 14 as amended recite the proper Markush format using the suggested phrase "selected from the group consisting of" and with the conjunction "and". Accordingly, applicants maintain that amended claims 12 and 14 particularly point out and distinctly claim the subject matter of the invention.

In view of these remarks, applicants maintain that claims 12 and 14 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the rejection be withdrawn.

**Rejection under 35 U.S.C. §102(b) and §103**

The Examiner rejected claims 2, 4, 7-8, 11, 13, 15-18 and 25 under 35 U.S.C. §102(b) as allegedly anticipated by or under 35 U.S.C. §103 as allegedly obvious over

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Schoolnik. Specifically, the Examiner alleges that the peptides and compositions of the subject invention are disclosed in Schoolnik.

Applicants respectfully traverse the Examiner's rejection, and respectfully disagree with the Examiner's interpretation of the teachings of Schoolnik. Schoolnik teaches HPV16 E6 and E7 peptides and HPV proteins which may be used to raise antibodies for diagnostic and therapeutic purposes. The subject invention, on the other hand, provides peptides comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein the amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV or HPV 18, and wherein the nonapeptide has the ability to bind in the grooves on top of the human major histocompatibility complex (MHC) Class I molecule, as well as pharmaceutical compositions comprising this nonapeptide. These features are recited in the claims. As stated above, the basis for this invention is applicants' discovery of HLA class I binding peptides of HPV16 and HPV18 with CTL inducing properties. Schoolnik does not disclose peptides comprising the claimed sequences combined with the claimed features of the peptides. In addition, Schoolnik does not disclose peptides which bind to the MHC Class I molecule or that are cytotoxic to T lymphocyte epitopes. Schoolnik discloses peptides which would induce a B-cell response, not a CTL response. In fact, Schoolnik does not disclose any of the peptides claimed in the instant invention.

Moreover, as mentioned above, the subject invention provides for inducing an immune response through T-cell mediated immunity. No antibodies are contemplated in this invention, only peptides presented to MHC-I to elicit an immune response have been envisaged. Schoolnik merely discusses the raising of antibodies to viral proteins, but does not illicit an immune response. The antibodies raised would presumably be used as a therapy to HPV related diseases. The T-cell mediated response and the antibody response are separate and distinct types of immunity. Schoolnik does not address,

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contemplate or suggest the T-cell mediated immunity through the presentation of the claimed peptides by MHC-I to illicit an immune response as is claimed in the subject invention. Accordingly, applicants maintain that amended claims 2, 4, 7-8, 11, 13, 15-16 and 25 define an invention patentable over the cited reference, and submit that the cited reference fails to set forth either a case of anticipation or a prima facie case of obviousness. The reference therefore cannot be said to anticipate or render obvious the claimed invention. In view of these remarks, applicants maintain that claims 2, 4, 7, 8, 11, 13, 15, 16 and 25 are patentable over Schoolnik, and that the rejections under 35 U.S.C. §102(b) and §103 should be withdrawn.

#### **Conclusion**

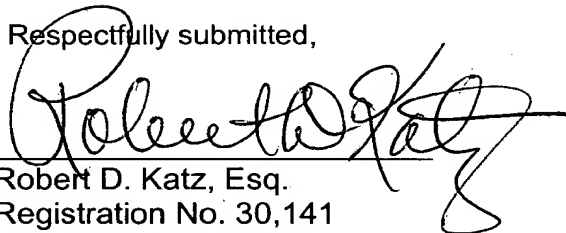
For the reasons set forth herein, applicants respectfully request that the Examiner reconsider and withdraw the rejections, and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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No fee is deemed necessary in connection with this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Robert D. Katz", written over a horizontal line.

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